Phosphodiesterase II, the cGMP-activatable cyclic nucleotide phosphodiesterase, regulates cyclic AMP metabolism in PC12 cells.

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Analysis of cyclic nucleotide phosphodiesterase (PDE) activity in cellular fractions from cultured rat pheochromocytoma (PC12) cells has shown that the predominant hydrolytic activity in both cytosolic and particulate compartments is characteristic of a PDE II, the cGMP-activatable family of PDE isozymes. Cytosolic PDE activity was purified to a high degree utilizing DE-52 anion exchange and cGMP-Sepharose affinity chromatographies. The physicochemical properties of PC12 PDE II were similar to those of PDE II isolated from particulate or soluble fractions of other tissues, including subunit molecular weight of approximately 102,000, activation of cAMP hydrolysis by cGMP, and positive cooperative kinetic behavior for cAMP and cGMP hydrolysis. The potential role of PDE II in regulating cAMP metabolism in intact PC12 cells was studied using an [3H] adenine prelabeling technique. Stimulation of PC12 cell adenosine receptors resulted in a 5-8-fold increase in cAMP accumulation. Removal of the adenosine stimulus by the addition of exogenous adenosine deaminase resulted in a rapid decay of cAMP to prestimulated basal levels within 2 min. Treatment of PC12 cells with atrial natriuretic factor or sodium nitroprusside caused 1) increased intracellular cGMP levels, 2) attenuation of adenosine-stimulated cAMP accumulation, and 3) increased rates of cAMP decay after removal of the adenosine stimulus. Treatment of PC12 cells with HL-725 (a potent inhibitor of isolated PDE II activity in vitro) caused 1) increased basal cAMP accumulation, 2) potentiation of adenosine-stimulated cAMP accumulation, and 3) retardation of the rate of cAMP decay after removal of the adenosine stimulus. HL-725 blocked both the attenuation of cAMP accumulation and the accelerated rate of cAMP decay observed with the cGMP-elevating agents. These results suggest that, in PC12 cells, drugs or hormones that inhibit PDE II or increase intracellular cGMP levels to activate PDE II can modulate cAMP metabolism by altering the catalytic status of the enzyme.

1: Pharmacol Biochem Behav 1999 May;63(1):185-92 Related Articles, Links

ELSEVIER SCIENCE FULL-TEXT ARTICLE

Behavioral effects of family-selective inhibitors of cyclic nucleotide phosphodiesterases.

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The effects of family selective inhibitors of phosphodiesterase (PDEI, PDE2, PDE3, PDE4, and PDE5) on the behavior of rats under either a differential-reinforcement-of-low-rate (DRL) 72-s schedule or a variable-interval (VI) 30-s schedule were determined; previous work has shown that antidepressant drugs increase reinforcement rate under long DRL schedules. The PDE4-selective inhibitor rolipram (0.03-0.1 mg/kg) reduced response rate and increased reinforcement rate under the DRL schedule in a dose-dependent manner; similar effects were observed with the tricyclic antidepressant drug desipramine (3-10 mg/kg). Both of these drugs produced biphasic effects on behavior maintained under the VI schedule, increasing response rate at the lower doses tested (rolipram: 0.003 mg/kg; desipramine: 0.03 mg/kg) and decreasing response rate at higher doses (rolipram: 0.1 mg/kg; desipramine: 0.3-18 mg/kg). Of the other PDE inhibitors tested, only the PDE5-selective inhibitor zaprinast (10 mg/kg) produced an antidepressant-like effect on DRL behavior. However, in contrast to the biphasic effects of rolipram and desipramine on VI behavior, zaprinast produced monotonic decreases in response rate (10-30 mg/kg). The PDE2-selective inhibitor trequinsin produced biphasic effects on response rate under the VI schedule, increasing rates at low doses (3-5.6 mg/kg) and decreasing rates at higher doses (18-30 mg/kg). Trequinsin also reduced response rate under the DRL schedule (30 mg/kg); however, the reduction in response rate was not accompanied by increased reinforcement rate. The PDE3-selective inhibitor milrinone (1-10 mg/kg) tended to increase response rates under both schedules while the PDE1-selective inhibitor vinpocetine did not affect behavior at the dose range tested (1-30 mg/kg). These findings suggest that inhibition of PDE4 results in a rather unique pattern of behavioral effects, most notably an antidepressant-like effect on DRL behavior. It remains to be determined if a similar effect produced by zaprinast also implicates PDE5 in the mediation of antidepressant activity or represents an effect of this drug on PDE4 activity

1: Blood Coagul Fibrinolysis 1990 Aug;1(3):247-58 Related Articles, Links

Arachidonic acid metabolites, ADP and thrombin modulate occlusive thrombus formation over extensive arterial injury in the rat.

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Platelet-dependent occlusive thrombosis at sites of deep vessel wall injury elicited by electrical stimulation of rat carotid arteries was significantly reduced by thromboxane A2 (TXA2) synthetase inhibition and/or TXA2/prostaglandin endoperoxide receptor antagonism (ridogrel 1.25 mg/kg i.v.; dazoxiben 5 mg/kg i.v.; sulotroban 20 mg/kg i.v.), by inhibition of ADP-dependent platelet responses (ticlopidine 3 x 200 mg/kg orally) and by anticoagulation (heparin 250 U/kg i.v.; warfarin 1.25 mg/kg i.p.). This points to an involvement of arachidonic acid metabolites, ADP and thrombin as modulators of the thrombotic process. The antithrombotic effect of ridogrel (IC50 = 0.22 mg/kg i.v.) was abolished by cyclooxygenase inhibition (suprofen 5 mg/kg i.v.) but enhanced by cAMP phosphodiesterase inhibition (HL 725 6 micrograms/kg/min i.v.), demonstrating the importance of platelet inhibitory prostanoids such as PGD2, and prostacyclin formed after TXA2 synthetase inhibition. High doses of ridogrel (1.25 mg/kg i.v.) producing additional TXA2/prostaglandin endoperoxide receptor antagonism were more effective than lower doses (0.16 mg/kg i.v.) providing TXA2 synthetase inhibition alone. The antithrombotic effect of ridogrel, when combined with ticlopidine or heparin, exceeded that of the single compounds, pointing to interactions between arachidonic acid metabolites, ADP and thrombin in the formation of occlusive thrombosis at sites of arterial injury.

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1: FEBS Lett 1988 Nov 7;239(2):367-70

Nerve growth factor increases the cyclic GMP level and activates the cyclic GMP phosphodiesterase in PC12 cells.

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Nerve growth factor (NGF) rapidly increases the cyclic GMP (cGMP) level about 2-3-fold and enhances the cGMP phosphodiesterase (PDE) activity about 2-fold in rat pheochromocytoma PC12 cells. No changes in the level of cyclic AMP (cAMP) and in the activity of cAMP PDE were found. GTP and a nonhydrolysable analog of GTP, GMP-PCP, at 100 microM, were able to mimic the effect of NGF on the cGMP PDE activity. These results suggest that the cGMP system may be one of the second messengers of NGF action in PC12 cells.

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